AD_____

Award Number: DAMD17-02-1-0501

TITLE: Immune Surveillance, Cytokines, and Breast Cancer Risk: Genetic and Psychological Influences in African American Women

PRINCIPAL INVESTIGATOR: Dana H. Bovbjerg, Ph.D.

CONTRACTING ORGANIZATION: Mount Sinai School of Medicine
New York, New York 10029-6574

REPORT DATE: August 2004

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	August 2004	Annual (22 Jul 2003 - 21 Jul 2004)

4. TITLE AND SUBTITLE
Immune Surveillance, Cytokines, and Breast Cancer Risk: Genetic and Psychological Influences in African American Women

5. FUNDING NUMBERS
DAMD17-02-1-0501

6. AUTHOR(S)
Dana H. Bovbjerg, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Mount Sinai School of Medicine
New York, New York 10029-6574

E-Mail: Dana.bovbjerg@mssm.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

Breast cancer cells are known to bear determinants that would allow tumor specific immune responses. However, initiation and amplification of such immune responses are critically dependent upon the balance in TH1 and TH2 cytokine profiles. This molecular epidemiological study evaluates the impact that variability in cytokine profiles, (inferred from functional polymorphisms in cytokine genes), may have on breast cancer risk among urban African-American women. In the first phase of the study, DNA collected and approved for additional study as part of a previously funded Case-Control investigation (n=1600) will be assessed for cytokine polymorphisms. Because cytokine profiles are also known to be affected by environmental factors, particularly levels of stress, this study also evaluates the relative contribution of genotype and stress influences using data collected for that purpose from a sub-sample of healthy Controls (n=400) recruited from the "graduates" of the larger study. Results will allow evaluation of the possibility that deficits in cytokine responses due to genetic or environmental factors may contribute to breast cancer risk. Based on these findings, women at risk for breast cancer because of polymorphisms in genes important to effective immune surveillance could be targeted for innovative prevention strategies including stress reduction and immune modulators.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Immune surveillance, cytokines, psychoneuroimmunology	6
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

Title: "Immune surveillance, cytokines and breast cancer risk: Genetic and psychological influences in African American women"

Principal Investigator: Dr. Dana H. Bovbjerg

INTRODUCTION:

This study tests the hypothesis that dysregulation of cytokine production profiles necessary for effective immune surveillance against transformed cells may contribute to increased risk of breast cancer. We hypothesize that women whose cytokine responses tend to favor humoral (Type 2) over cell-mediated (Type 1) responses are at risk for developing breast cancer. Because assessments of cytokine responses in blood samples from patients are likely to be affected by the presence of clinical disease and its treatment, we will test this hypothesis using a molecular epidemiologic approach. In the context of a previously funded case-control study (n=1600), we will evaluate the role of polymorphisms in cytokine genes associated with dysregulation in relation to breast cancer risk. We will also explore the relative contribution of genotype (cytokine polymorphisms) and environmental influences (e.g., stress-induced immune modulation) to cytokine responses in a sub-sample of healthy control subjects (n=400).

The study is linked to a project (Ambrosone, PI) approved for funding as part of a Behavioral Center of Excellence award from the Army (DAMD-17-01-1-0334, Bovbjerg, PI). The "parent" project draws on collaborations with physicians at the NYC hospitals that have the largest referral patterns for African-Americans in Manhattan, Bronx, Brooklyn and Queens to recruit newly diagnosed African-American breast cancer patients. Age-matched controls are selected using Random Digit Dialing (RDD). Patients consenting to participate in the study (n=1600) undergo an interview and provide a blood specimen for DNA extraction. For the piggy-backed study, appropriate banked DNA will be genotyped for the cytokine polymorphisms of interest. Additional newly obtained blood specimens from consenting Control participants (n=400) will be processed for cytokine responses (phenotype), and an additional set of questionnaires focused on psychological stress will be completed. Data analyses will be conducted using standard approaches.

This study synthesizes concepts from behavioral research and molecular epidemiology to address critical questions regarding breast cancer etiology. By exploring hypotheses related to psychoneuroimmunology and using technology and paradigms from molecular epidemiology, this research may make important contributions to identifying causes of breast cancer so that it may be eradicated. By examining case-control differences in cytokine polymorphisms, the role of this aspect of immune function in breast cancer may be elucidated. Furthermore, the evaluation of stress effects on cytokine responses in vitro, particularly in relation to genotype, may suggest a mechanism and provide stronger support for a possible role of stress in breast cancer etiology.

BODY:

The "parent" project, DAMD-17-01-1-0334, (Human Subjects Protection Scientist, Dr. Maryann Pranulis), was recommended for approval in April 2004, however, we have yet to receive notification of HSRRB approval for this Project (Human Subjects Protection Scientist, Dr. Maryann Pranulis). As the "parent" study will be the entry point for recruitment for participants in this study, we could potentially be collecting data at this time. We therefore continue to fall substantially behind our anticipated timeline for completion of the tasks listed in the Statement of Work. In our last correspondence with Dr. Pranulis, she indicated that approval of this study was dependent upon the approval of the "parent" project, but gave no indication that it has as yet been formally reviewed by the HSRRB.

In our last report, we proposed a modification of the original Statement or Work to include a new Task (Months 0-18): Successful application for HSRRB approval through the USAMRAA office. We now propose to modify that Task (Months 0-36): Successful application for HSRRB approval through the USAMRAA office. Given the 2-10 month time period required for turn around of similar materials by the HSRRB of the USAMRAA after previous submissions for other funded projects of ours that have been submitted to Dr. Pranulis, we anticipate approval by 2005.

In the absence of approval by the HSRRB of the USAMRAA, we have focused our energies on completion of required local Institutional Review Board requirements (most recently approved by Mount Sinai School of Medicine 7/21/04), as well as Task 1: Setting up of study procedures of our funded Project. We have trained research assistants and confirmed reliability; we have produced study questionnaires; we have established procedures for coordination with the "parent" project; we have established procedures for coordination with the Recruitment, Tracking, and Interviewing Core of the "parent" Behavioral Center of Excellence (Bovbjerg, PI). This groundwork should enable us to move quickly to the next Tasks, as soon as approval from HSRRB is obtained. As we have husbanded our resources, we anticipate being able to address all proposed Tasks in a timely manner after approval by the HSRRB of the USAMRAA. Recognizing the late start date, and an anticipated request of a no-cost extension of the Center and this project, we propose to modify the timeline of program of work to delay the start date for Tasks 2-7 by 28 months and the end dates by 24 months.

KEY RESEARCH ACOMPLISHMENTS:

At this point in the research, with no approval by the HSRRB of the USAMRAA, no results are yet available.

REPORTABLE OUTCOMES:

At this point in the research, with no approval by the HSRRB of the USAMRAA, no reportable outcomes are yet available.

CONCLUSIONS:

At this point in the research, with no approval by the HSRRB of the USAMRAA, no results are yet available. If the results of the proposed research are consistent with study hypotheses, the study could have profound implications for the eradication of breast cancer. The results of the proposed research may suggest new means of evaluating genetic risk of breast cancer in healthy women, as well as novel intervention strategies for long term reduction of that risk, including stress reduction, as well as biological response modifiers designed to ameliorate dysregulation of cytokine profiles.

REFERENCES:

N/A

APPENDICES:

N/A